

**PROVEN GLOBAL CONTRACT RESEARCH EXPERTISE  
FROM DISCOVERY THROUGH CLINICAL SUPPORT**

## **Custom Test Systems**

**Presented by:**  
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Director of Products

**July 27, 2021**

## XenoTech (XT):

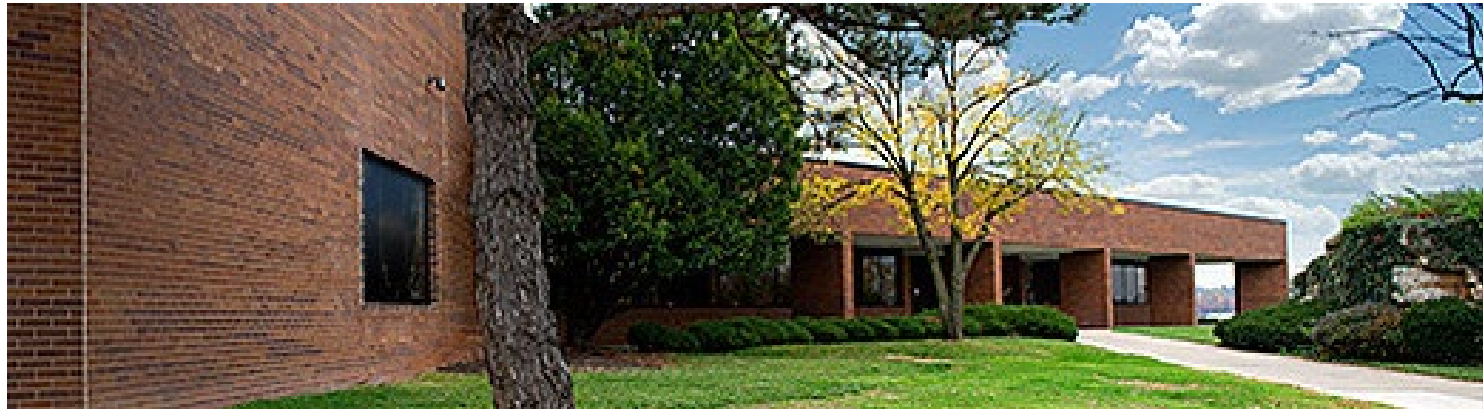
Contract Research Organization (CRO) founded in 1994

Provide high-quality *in vitro* test systems since 1995

Over 25 years experience in preparing subcellular fraction and hepatocyte test systems

Over 19 years of dedicated Custom Product staff

Provide test systems to pharmaceutical, government, chemical, agricultural, academic, animal health, and cosmetic organizations



# Cus•tom Pro•duc•ts

/ˈkɛstəm/ /ˈprädɛkt/

## *Noun*

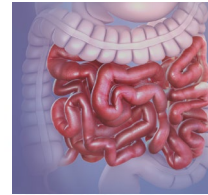
1. Unique or one-of-a-kind items that intimately involves customer input in the material selection, design, and individualized fit.
  2. Department of XT dedicated to providing unique products to meet client needs
- Anything that is not offered in our catalog.
  - Products made with various buffers, animal strains and tissues.
  - Client-provided procedures/processes
  - Non-typical subcellular fractions and membranes
  - Requested by clients for use at their location or by SXT Service groups for internal studies.

# History of XT Custom Products



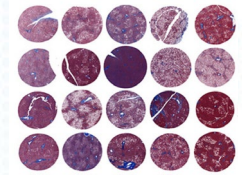
**1996:** XT offers 25 products derived from liver tissues

**2000:** R&D begins on extra-hepatic test systems



**2004:** Intestine products added to standard catalog

**2015:** Rat tritosomes added to standard catalog



**2018:** Human Tissue Research Biobank launches

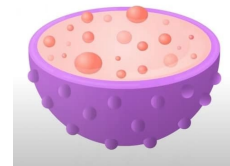
**1999:** First request for custom pooled HLM



**2002:** Dedicated Custom and Extrahepatic Department established

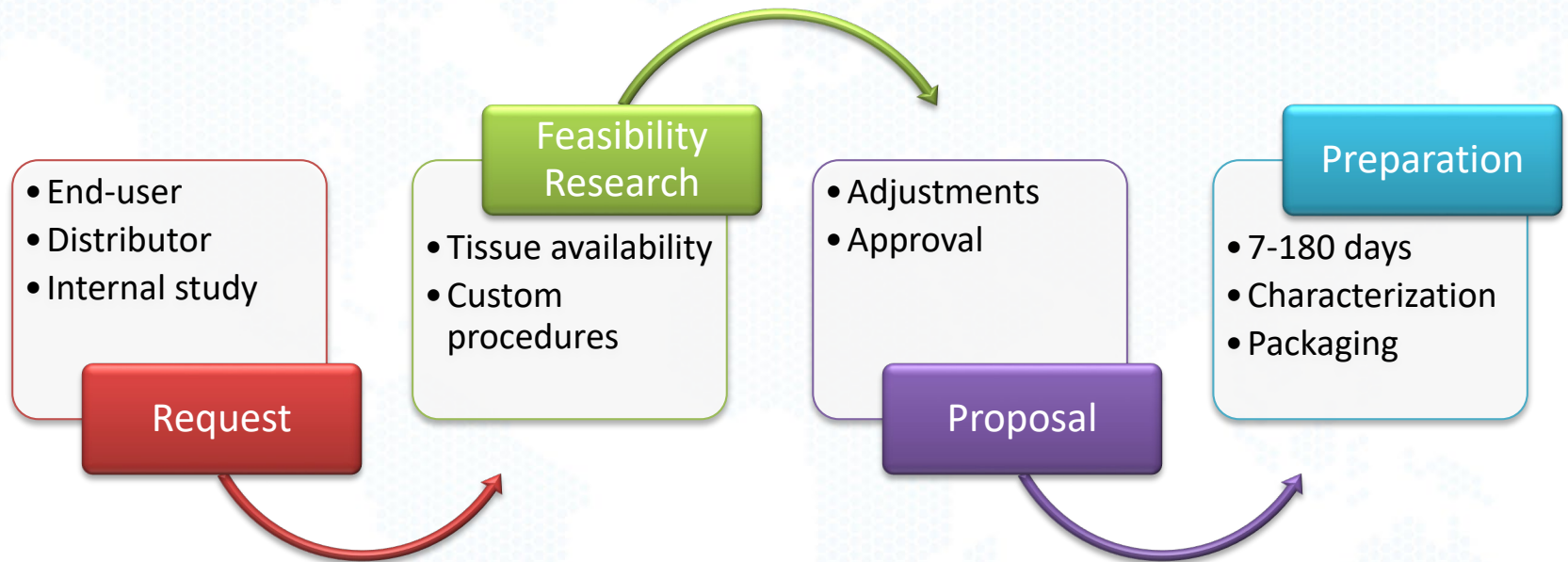
**2010:** Skin products added to standard catalog

**2017:** Human liver lysosomes added to standard catalog





## Custom Product Process



# Custom Product Examples

Species	<p>African Green Monkey B6C3F1 Mouse B6SJLF1 Mouse Balb/c Mouse Beagle Dog Brown Norway Rat C57BL/6 Mouse Cat CD-1 Mouse Chicken Cow Cynomolgus Monkey Db/db Lean Mouse</p>	<p>Db/db Obese Mouse Fischer 344 Rat Fox Chase SCID Mouse FVB Mouse GK Rat Goat Golden Syrian Hamster Gottingen Minipig Hanford Minipig Hartley Guinea Pig Horse Housefly</p>	<p>Human Japanese White Rabbit KK.Cg.Ay/J Mouse KK/HIJ Mouse Lewis Rat Long-Evans Rat Marmoset Monkey Mongolian Gerbil New Zealand RabbitNu/Nu Nude Mouse Ob/ob Lean Mouse</p>	<p>Ob/ob Obese Mouse Owl Monkey Pig Rhesus Monkey SCID Mouse Sheep Swiss Webster Mouse Wistar Han Rat Yucatan Minipig ZDF Lean Rat ZDF Obese Rat</p>
Tissues	<p>Adipose Tissue Adrenal Gland Blood Plasma Brain Cerebral Spinal Fluid Colon</p>	<p>Duodenum Eye Heart Ileum Jejunum Kidney</p>	<p>Liver Lung Muscle Ovary Pancreas Prostate</p>	<p>Skin Spleen Stomach Testes Thyroid Whole Blood</p>
Test Systems	<p>Brushborder Membrane Cytosol Eluate Extracts Hepatocytes</p>	<p>Homogenate Lysate Lysosomes Mast Cells Microsomes</p>	<p>Mitochondria Mucosa Non-parenchymal Cells Pre-lysate RNA</p>	<p>S9 Fraction Tissue (blocks and slides) Tritosomes Unprocessed Tissue</p>

# Our Goal is to Meet and Exceed the Customer's Needs

*Standard offerings are not always compatible with client needs or unique research*

- Unparalleled experience developing specialized techniques to provide dependable preparations yielding quality data
- Dedicated department for custom preparations with expertise in working with difficult or delicate tissues and procedures
- No minimum set-up fee
- No-fee feasibility research, pricing and proposal generation
- **Customer satisfaction is #1 priority**





## Question #1





## Custom Project Size Varies



Single Vial



Tens of thousands of vials

# Custom Designed Pools



## Meet Customer's Unique Requirements

- Enzyme activities / Customized buffers or prep
- Large enough batch to meet multi-year needs



## Design pool

- Theoretical vs Actual activities
- Specified enzyme activity optimized



## Preparation/Processes

- Coordinate multi-week preparation and characterization
- Packaging and shipping



## 2015: XT's Largest Custom Product Project

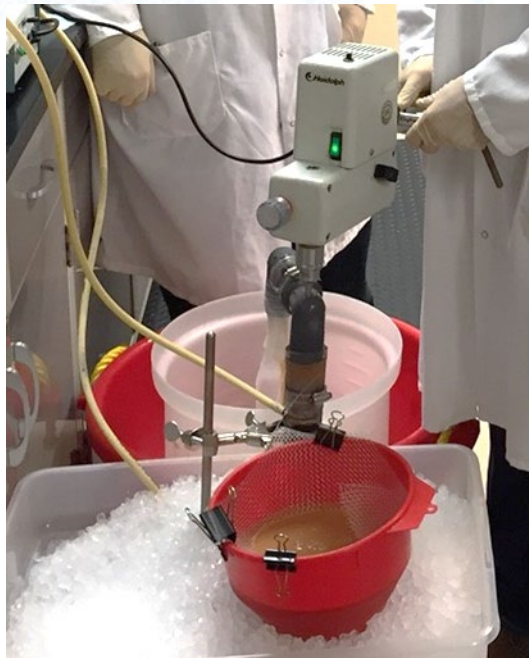
- Pool of 50 Donors
- Matching Microsomes, S9 and Cytosol
- Kinetic Constant ( $V_{max}$  and  $K_m$ ) characterization over multiple days for 14 CYPs and UGTs
- CYP genotype data for all 50 donors
- DNA isolates provided

**Total Vials Delivered: >50,000**





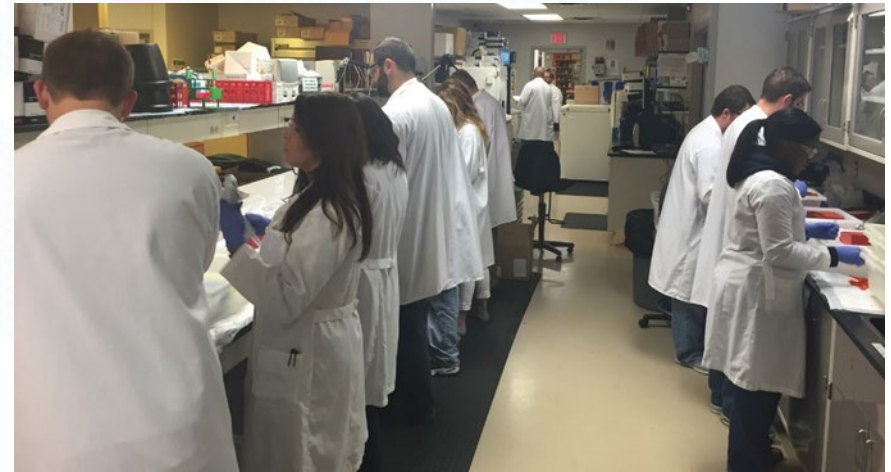
## 2015: XT's Largest Custom Product Project



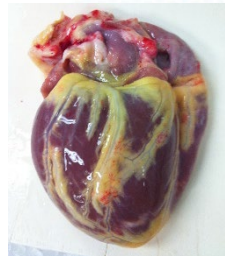
- Custom designed continuous flow homogenizer.
- Increases preparation efficiency by 300%
- Decreases production costs – passed on to customer

## 2015: XT's Largest Custom Product Project

- Total of 22 scientists involved
- Over 2000 hours
- Provided final characterized pool within three months
- Ten-year supply of subcellular fractions for client



# Challenges of Extrahepatic Tissues





# Challenges of Extrahepatic Tissues

Homogenization  
challenges



Proteases and  
extracellular  
interference





# Challenges of Extrahepatic Tissues

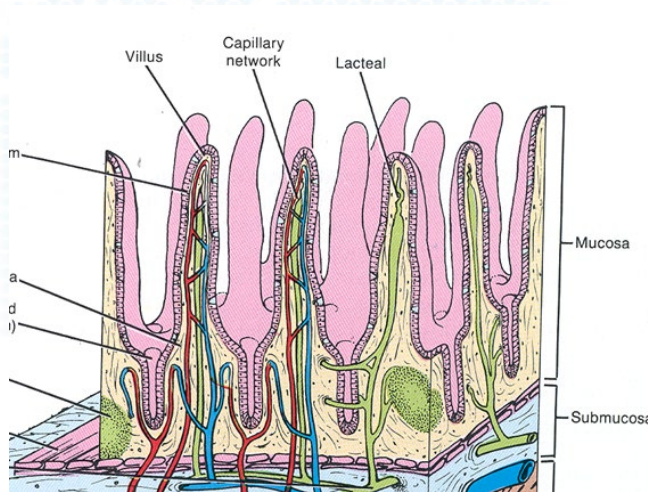
## Homogenization challenges



## Cryomill



# Challenges of Extrahepatic Tissues



Proteases and  
extracellular  
interference

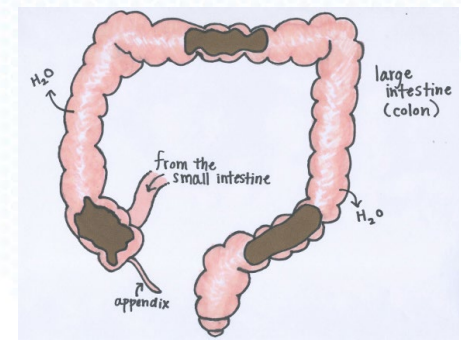
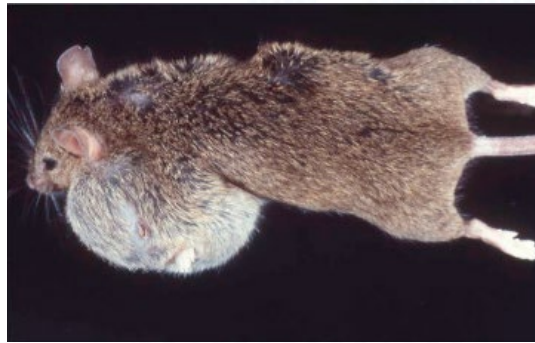




## Question #2



## No Request is Too Unusual





## Non-CYP or UGT Enzymes of Interest

Aldehyde Oxidase



Xanthine Oxidase

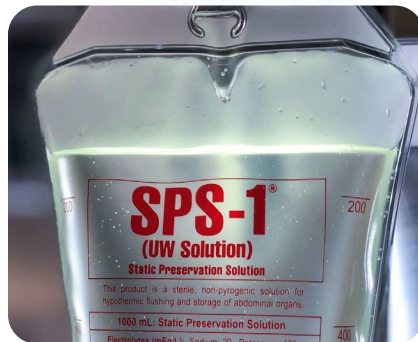


## Non-CYP or UGT Enzymes of Interest

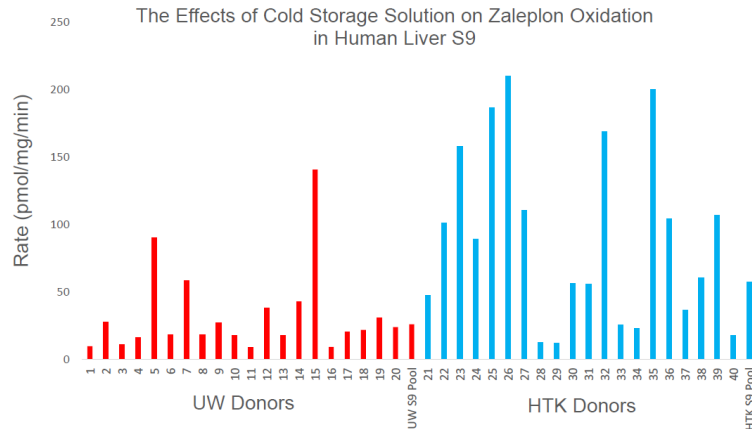
Pools of Human liver S9 and Cytosol exhibited lower than expected AO/XO activity

Sample pools made with adjustments of buffer constituents, including removing EDTA

None of the buffers used were inhibiting AO/XO activity

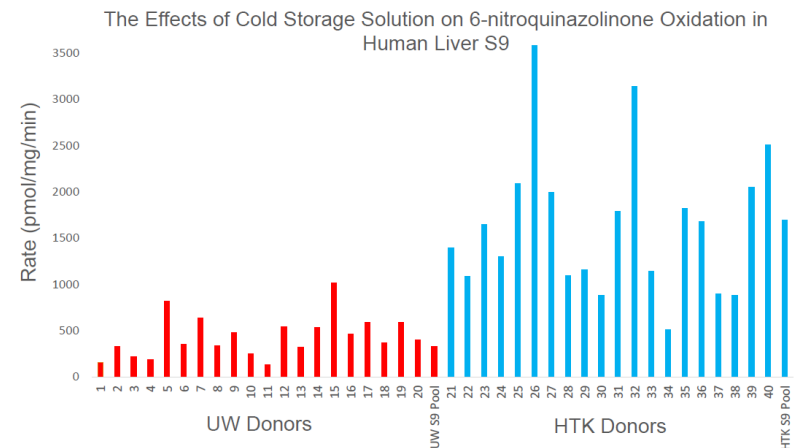


# Non-CYP or UGT Enzymes of Interest



## Aldhyde Oxidase Activity

## Xanthine Oxidase Activity



# Customized CryostaX Pooled Hepatocytes



Pools can be designed based on:

- Specific Enzyme Activity
- Pool Size
- BMI
- Disease State
- Age/Ethnicity/Gender
- Alcohol, Tobacco and/or Drug Use
- Serologies

Custom pools can be prepared easily, and easy means quickly at no additional cost



AA Human Liver Donors	
African-American HLM-07072008	
Alcohol Users - Individual HLM	
Available Hepatocytes and Corresponding Microsome and Liver Tissue	15Apr2013
Available Individual HLM - Smokers	
Available Individual HLS9 Samples	
Available Individu	Human Liver Microsome Activities from Diabetic Donors
CytoSta CYP2D6	Human Liver Microsomes 06Aug2013 with Diabetes Info
CYP2D6 HLM	Human Liver Microsomes from Diabetic Donors 5Feb2015
CYP3A5 genotyp	Human Liver Microsomes from Diabetic Donors 6Apr2015
Diabetic and Non	Human Liver Microsomes from Diabetic Donors 17December2015
Diabetic and Non	Human Liver Microsomes from Diabetic Donors 18Dec2015
Diabetic Donors C	Human Liver Microsomes from Diabetic Donors 19Apr2016
Diabetic Donors	Human Liver Microsomes from Nondiabetic Donors 5Feb2015
Diabetic Human I	Human Liver Microsomes from Nondiabetic Donors resembling Type II Diabetic Donor Demographics 20Feb15
Diabetic Human I	Human Liver Mic
Diabetic Human I	Individual HLM with UGT Activity (Specifically UGT2B7)
Diabetic Human I	Individual HLM
Diabetic Human I	Human Liver Mic
Diabetic Human I	Individual HLM-Average UGT1A9 Activity
Diabetic Human I	Human Liver S9 f
Diabetic Human I	Individual HLMS
Diabetic Human I	Human Liver San
Diabetic Human I	Individual HLS9 - Age 65 and Older
Diabetic Human I	Human Liver Tiss
Diabetic_Human I	Individual HLS9 - Ages 2-17
Diabetic_Non-Dia	HLM Ages 0-5
Diabetic-Nondiab	Individual HLS9 - Ages 10-18
Diabetic-Nondiab	HLM Ages 0-5_2
Diabetic-Nondiab	Individual HLS9 061808
Diabetic-Nondiab	HLM Ages 6-18
Diabetic-Nondiab	Individual HLS9 121307
Diabetic-Nondiab	Ind HLM - Low 2i
Diabetic-Nondiab	Individual HLS9 samples 11Feb11
Diabetic-Nondiab	Ind HLM Low 2Di
Diabetic-Nondiab	Individual Human Donors with Tissue Available from Select Ages 1Nov2011
Donor Demograp	Indiv HLM 10 31 i
Donor Informatio	Individual Human Intestinal Microsomes - 3-Jun-2009
Donors with vials	Individual Human Intestinal Microsomes - 15-Sep-2009
FMO and CYP3A I	Individual Human Intestinal Microsomes - 29-Jul-2009
Genotyped Huma	Individual Human Intestinal Microsomes - 30-Sep-2009
Hepatocytes with	Individual Human Intestine Cytosol 22Sep2014
High CYP2C9 an	Individual Human Intestine Cytosol 20Jun2013
High CYP2C19 as	Individual Human Intestine Microsomes 22Sep2014 with Vials Available
High CYP3A Indv	Individual Human Intestine Microsomes 22Sep2014
HLM - African An	Individual Human Intestine S9 09Mar19
HLM - Caucasian	Individual Human Intestine S9 25Apr2012
HLM - Low CYP2E	Individual Human Kidney Microsomes 15Nov2010
HLM High CYP2E	Individual Human Kidney Microsomes 27Jan2014
Human Asian Dor	Individual Human Liver African American Donors 5May15
	Individual Human Liver African American Donors URI 05Feb16
	Individual Human Liver Asian Donors that could be Prepared to S9, Cytosol and Microsomes 7Oct13
	Individual HLM -
	Individual Human Liver Caucasian Donors 13May15
	Individual HLM -
	Individual Human Liver Characterization Data for URI 18Sep13
	Individual HLM -
	Individual Human Liver Cytosol - 27Jan2020
	Individual HLM 0
	Individual Human Liver Cytosol 11Jan16
	Individual HLM A
	Individual Human Liver Cytosol 15May15
	Individual HLM A
	Individual Human Liver Cytosol and Microsomes
	Individual Human Liver Cytosol Demographics 13Feb14
	Individual Human Liver Cytosol Demographics 22Sep2014 with Vials Available
	Individual Human Liver Cytosol Demographics 22Sep2014
	Individual Human Liver Cytosol Samples
	Individual Human Liver Cytosol Samples-Replacement
	Individual Human Liver Cytosol with Flush Solution 13Jan15
	Individual Human Liver Cytosol
	Individual Human Liver Donor Information URI 29Nov18
	Individual Human Liver Donors - Donors 2-18 Years of Age (Procurement Agency)
	Individual Human Liver Donors - Donors 2-18 Years of Age with Characterization Data

# Custom Characterization

## Characterization Assays

### **Content**

Total P450 content by spectral analysis  
 Cytochrome  $b_5$  content by spectral analysis  
 NADPH-cytochrome c reductase activity

### **Cytochrome P450 activity**

7-Benzoxoresorufin O-dealkylation  
 7-Ethoxoresorufin O-dealkylation  
 7-Methoxoresorufin O-dealkylation  
 7-Pentoxoresorufin O-dealkylation  
 7-Ethoxycoumarin O-dealkylation  
 Phenacetin O-dealkylation  
 Coumarin 7-hydroxylation  
 Bupropion hydroxylation  
 Amodiaquine N-dealkylation  
 Diclofenac 4'-hydroxylation  
 S-Mephenytoin 4'-hydroxylation  
 Dextromethorphan O-demethylation  
 Chlorzoxazone 6-hydroxylation  
 Ebastine hydroxylation  
 Testosterone 2 $\alpha$ -hydroxylation  
 Testosterone 2 $\beta$ -hydroxylation  
 Testosterone 6 $\beta$ -hydroxylation  
 Testosterone 7 $\alpha$ -hydroxylation  
 Testosterone 15 $\alpha$ -hydroxylation  
 Testosterone 16 $\alpha$ -hydroxylation

### **Cytochrome P450 activity continued...**

Testosterone 16 $\beta$ -hydroxylation  
 Midazolam 1'-hydroxylation  
 Lauric acid 12-hydroxylation  
 4-Nitrophenol hydroxylation  
 Tolbutamide hydroxylation

### **UDP-Glucuronosyltransferase activity**

4-Methylumbelliferone glucuronidation  
 17 $\beta$ -Estradiol 3-glucuronidation  
 Trifluoperazine glucuronidation  
 1-Naphthol glucuronidation  
 Propofol glucuronidation  
 Morphine 3-glucuronidation  
 Chenodeoxycholic acid 24-glucuronidation  
 Testosterone 17-glucuronidation  
 7-Hydroxycoumarin glucuronidation  
 7-Hydroxycoumarin sulfonation

### **Monoamine oxidase activity**

5-Hydroxytryptamine oxidation  
 4 (Dimethylamino)benzylamine oxidation

### **Carboxylesterase activity**

Clopidogrel hydrolysis  
 Methylprednisolone 21-hemisuccinate hydrolysis

### **Glutathione S-transferase activity**

1-Chloro- 2,4-dinitrobenzene-glutathione conjugation

### **N-Acetyltransferase activity**

p-Aminobenzoic acid acetylation  
 Sulfamethazine acetylation  
 Dapsone acetylation

### **Aldehyde Oxidase**

Phthalazine oxidation

### **Lysosomal Enzymes**

Acid Phosphatase  
 RNase  
 Cathepsin B

### **Marker Substrate Enzymatic Fold Induction**

CYP1A2  
 CYP2B6  
 CYP3A4


### **Uptake Transporter**

OATP1B1  
 OATP1B3  
 OCT1  
 NTCP

# Custom Products *can become* Standard Products

- Consistent requests for custom products are evaluated for addition to standard product catalog
- Our catalog offerings evolve with client needs
- This process has assisted in a 14-fold growth of standard products

1996  
25 Catalog Products








2021  
350 Catalog Products

**80% attributed to repeat  
custom product requests**



# Not in the catalog? Not the end of the road

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Don't see what you're looking for?  
A Custom Product may be the solution



## Question #3

**PROVEN GLOBAL CONTRACT RESEARCH EXPERTISE  
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# **Thank You!**

# **Questions?**